Remarks

Upon entry of the present amendment, claims 9, 11, and 13-23 will be pending. Claim 11 has been withdrawn by the Examiner. Applicants thank the Examiner for indicating that claim 11 will be rejoined once the present claims are found allowable.

Applicants have canceled claims 1, 10, and 12 without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter encompassed by all canceled claims in one or more divisional or continuation applications. Claims 9, 14, 16, and 21 have been amended to delete the recitation "about" from the claims. In addition, claim 9 has been amended to add "wherein said I-FLICE-2 polypeptide inhibits TNFR-1 and CD-95 induced apoptosis" and to add a ";" as requested by the Examiner. Support for these amendments can be found in the specification, for example, at page 25, paragraph 86; at page 30, paragraph 108.

Applicants have also updated the priority information in the first paragraph of the specification as requested by the Examiner. Thus, no new matter has been added.

I. Enablement Rejections Under 35 U.S.C. § 112, First Paragraph

a. The Examiner has rejected claims 9, 18, 20, 22, and 23 under 35 U.S.C. § 112, first paragraph for alleged lack of enablement in that the claims allegedly fail to comply with the deposit requirement rules. In particular, the Examiner alleges that "it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification." *See*, page 4, section 8.

In response, Applicants' representative hereby gives the following assurance by signature below:

Human Genome Sciences, Inc., the assignee of the present application, has deposited biological material under the terms of the Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for the Purposes of Patent Procedure with the following International Depository Authority: American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209 (present address). The deposit was made on May 15, 1997, accepted by the ATCC, and given ATCC Accession Number 209038. In accordance with M.P.E.P. § 2410.01 and 37 C.F.R. § 1.808, assurance is hereby given that all restrictions on the availability to the public of ATCC Accession Number 209038 will be

irrevocably removed upon the grant of a patent based on the instant application, except as permitted under 37 C.F.R. § 1.808(b). A partially redacted copy of the ATCC Deposit Receipt for Accession Number 209038 is enclosed herewith as Exhibit A.

Applicants submit that the rejections under 35 U.S.C. 112, first paragraph, have been overcome or obviated by the above amendments and statements. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

b. The Examiner has also rejected claims 9, 13-17, and 19-23 under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. In particular, although the Examiner asserts that the specification is enabling for an isolated I-FLICE-2 polypeptide comprising amino acids 1 to 348 of SEQ ID NO:6, the Examiner alleges that "[g]iven the ambiguity of the specified amino acid residues, there is insufficient guidance as how to make at least 95% sequence identity to the said polypeptide." *See*, pages 5-8, section 9.

Applicants respectfully disagree and traverse this rejection.

To satisfy the enablement requirement, the specification must enable a person of ordinary skill in the art to practice a single use of the claimed polypeptides without undue experimentation. *See, e.g.*, MPEP §2164.01(c). To make a proper enablement rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. MPEP §2164.04; *see also, In re Wright*, 999 F.2d 1557, 1561-1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Applicants respectfully submit that the Examiner has not provided sufficient evidence or a basis to question the enablement provided in the specification for the claimed polypeptides.

The Examiner has cited several papers in support of the position that functional assignments based on sequence structure or similarity are unpredictable and unreliable. In particular, the Examiner relies on Ngo et al. to support the proposition that "the relationship between the amino acid sequence of a protein (polypeptide) and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable." *See*, section 9, page 6, fourth paragraph. Similarly, the Examiner relied on Attwood et al. and Skolnick et al. in support of the proposition that functional prediction based on sequence and structure is unpredictable. However, all of these references discuss the limitations of using computational analyses in assigning function to genomic sequences based on similarity found through searching known databases of genes. They do not address nor question the predictability of making a variant with a particular percent identity and testing it for a known

activity. Thus, these references fail to support the assertion that the claimed polypeptides are not enabled.

The Examiner has further cited Mikayama et al. in support of the proposition that "even single amino acids changes ... can have dramatic effects on the protein's function." *See*, section 9, page 7, first paragraph. Applicants respectfully disagree with the Examiner's contention.

While this proposition may be true for very specific amino acid changes in the particular protein – human GIF – which is the subject of the reference, Applicants note that Mikayama et al. does not discuss whether changes at *any other* of the 114 positions alter the biological activity of GIF. Thus, the observations of Mikayama et al. relating to a particular GIF amino acid position do not necessarily extend to all other amino acid positions in GIF, much less to positions in other proteins such as I-FLICE-2. Therefore, the cited reference fails to support the assertion that any and all amino acid changes in I-FLICE-2 would have a dramatic effect on activity.

Even assuming arguendo that the situation reported in Mikayama is representative of all amino acid positions in GIF, it is not representative of all proteins *or* all amino acid substitutions, deletions, and insertions. Numerous publications in the art support the contention that, in general, proteins are resilient to modification and retain functional activity notwithstanding numerous amino acid substitutions, deletions, and insertions. For example, the specification discloses that Bowie, J.U. et al., "Deciphering the Message in Protein Sequencing: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990) provides guidance concerning how to make phenotypically silent amino acid substitutions. *See*, specification, for example, at page 15-16, paragraph 48; and at page 18, paragraph 59.

A further example of the tolerance of proteins to amino acid modification is provided by Gayle et al., "Identification of regions in Interleukin-1α important for activity," J. Biol. Chem. 268(29):22105-22111(1993) (submitted herein as Exhibit B). This reference discloses the use of random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Thus, the art generally recognizes the resiliency of proteins in retaining their functional activity upon modification.

In addition, the Federal Circuit has held that making the claimed species and screening them for function is acceptable, as long as the experimentation is not undue. As in all cases, this is the test: whether it would require undue experimentation to practice the invention – even when a claim might encompass some inoperative embodiments. *See generally, Atlas Powder v. E.I. Du Pont de Nemours & Co.* 750 F.2d 1569, 224 U.S.P.Q. (BNA) 409 (Fed. Cir. 1984). Therefore, it is clearly not *per se* undue to make polypeptides that are 95% identical to the claimed amino acid sequences of SEQ ID NO:6 and then test these variants for the ability to inhibit TNFR-1 and CD-95 induced apoptosis, particularly when specific guidance was clearly disclosed in the specification coupled with what was known in the art at the time the invention was filed. Moreover, such guidance need not be provided through working examples in the specification. *See*, M.P.E.P. § 2164.02 at 2100-187.

Applicants contend that ample guidance is provided in the specification on how to make, test, and use the claimed polypeptides to inhibit TNFR-1 and CD-95 induced apoptosis. For example, the specification teaches that I-FICE-2 polypeptides of the invention and variants thereof are capable of inhibiting TNFR-1 and CD-95 induced apoptosis. See, specification, for example, at page 3, paragraph 5; at page 4, paragraph 9; at page 7-8, paragraph 23; and at page 18, paragraph 59. The specification further teaches how to make, screen, and use the claimed polypeptides.

In addition to the amino acid sequence common to the polypeptides of the claimed invention (e.g., SEQ ID NO:6), the specification further provides ample disclosure of other relevant characteristics of the claimed polypeptides. First, the specification provides the parameters used to determine the percent identity of the polypeptides of the claimed invention. *See*, for example, specification at page 21, paragraph 67 to page 22, paragraph 71. The specification further provides a detailed analysis of the structural attributes of the I-FLICE-2 protein, including important domains of the protein. *See*, for example, specification at page 7, paragraph 23. Moreover, the specification provides guidance on how to make variants which fall within the scope of the instant invention by insertion, deletion, inversions, repeats, and type substitutions. *See*, specification, for example, at page 18, paragraph 59 to page 22, paragraph 71. The specification also provides a detailed analysis of the functional

attributes of the I-FLICE-2 protein, such as, for example, antigenic index of the I-FLICE-2 polypeptide. *See*, specification, for example, at page 5, paragraph 17; and at Figure 5. Thus, the specification provides ample direction to the skilled artisan as to which amino acids of SEQ ID NO:6 are suitable to modify without substantially affecting activity.

Additionally, the specification also teaches the skilled artisan how to screen these variants for the ability to inhibit TNFR-1 and CD-95 induced apoptosis. In particular, the specification teaches a cell death assay useful for measuring the apoptotic activity of I-FLICE-2 polypeptides. See, specification, for example, at page 5, paragraph 18; at page 15, paragraph 46, at Example 6, page 54, paragraph 192 to page 55, paragraph 194.

Accordingly, Applicants submit that the teachings of the specification, in combination with the level of skill in the art, enable a skilled artisan to make by substitution, deletion and insertion, polypeptides that are 95% identical to the claimed amino acids SEQ ID NO:6 without changing the anti-apoptotic activity of the protein; to screen said polypeptides for anti-apoptotic activity; and to use said polypeptides in inhibiting TNFR-1 and CD-95 induced apoptosis. Thus, Applicants submit that one of skill in the art would be able to routinely make and use the invention commensurate in scope with the claims. Any experimentation, if necessary, would not be undue. Accordingly, Applicants respectfully request that the Examiner's rejection of the claims 9, 13-17, and 19-23 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

II. Written Description Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 9, 13-17, and 19-23 under 35 U.S.C. § 112, first paragraph for alleged lack of written description. In particular, the Examiner alleges that

> [w]ith the exception of the specific isolated I-FLICE-2 comprising SEQ ID NO:6 or an Fc fusion protein comprising SEQ ID NO:6, there is [in]adequate written description about the structure associated with function of all polypeptide having an amino acid sequence at least 95% identical to amino acid sequence selected from the group consisting of: (a) amino acids from about 1 to about 75 in SEQ ID NO:6; (b) amino acids from about 76 to about 252 in SEQ ID NO:6; (c) amino acids from about 253 to about 348 in SEQ ID NO:6; (d) amino acids from about 1 to about 348 in SEQ ID NO:6; (e) amino acids from about 2 to about 348 in SEQ ID NO:6 without the amino acid sequence.

See, pages 8-9, section 10.

Applicants respectfully disagree and traverse this rejection.

Although Applicants do not acquiesce to the Examiner's argument, Applicants have amended claims 9, 14, 16, and 21 to delete the recitation of "about". Accordingly, the Examiner's argument that "the term 'about' extends the upper and lower limits of the amino acids residues in SEQ ID NO:6" is rendered moot.

Additionally, Applicants have amended claim 9 to recite "wherein said I-FLICE-2 polypeptide inhibits TNFR-1 and CD-95 apoptosis." For the reasons provided below, Applicants believe that the claims, both as amended and as rejected, are fully described in the instant application.

The test for the written description requirement is whether one skilled in the art could reasonably conclude that the inventor has possession of the claimed invention in the specification as filed. (*See*, M.P.E.P. § 2163(I) at 2100-15, and *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991)).

The Federal Circuit has re-emphasized the well-settled principle of law that "[t]he written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed,'" *Union Oil Company of California v. Atlantic Richfield Company*, 208 F.3d 989, 54 U.S.PQ.2d 1227 (Fed. Cir. 2000). Further, the Federal Circuit has emphasized the importance of what the person of ordinary skill in the art would understand from reading the specification; and not whether the specific embodiments had been explicitly described or exemplified. Indeed, the court noted that "the issue is whether one of skill in the art could derive the claimed ranges from the patent's disclosure." *Union Oil Company of California v. Atlantic Richfield Company*, 208 F.3d at 1001, (emphasis added).

Thus, the Examiner bears the initial burden of presenting a *prima facie* case of unpatentability based on lack of written description by presenting evidence or reasons why one skilled in the art would *not* reasonably conclude that Applicants possessed the subject matter as of the priority date of the present application. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ2d 90, 96 (C.C.P.A. 1976); M.P.E.P. § 2163.04. In the instant case, the Examiner has not met this burden because the specification describes with reasonable clarity the claimed subject matter such that one of skill in the art would reasonably conclude that the inventors were in possession of the claimed subject matter on the earliest filing date of the present application.

In particular, Applicants submit that the specification provides ample written description to enable one of skill in the art to visualize or recognize the identity of the members of the claimed genus. For example, the specification provides the skilled artisan with the detailed structure of the polypeptides of the invention, *e.g.*, the amino acid sequence of I-FLICE-2 disclosed in SEQ ID NO:6. *See*, for example, specification at page 5, paragraph 16; at page 7, paragraph 22; at page 18, paragraph 57; and at Figures 4A-4C.

In addition to the amino acid sequence common to the polypeptides of the claimed invention (e.g., SEQ ID NO:6), the specification further provides ample disclosure of other relevant characteristics of the claimed polypeptides. First, the specification provides the parameters used to determine the percent identity of the polypeptides of the claimed invention. *See*, for example, specification at page 21, paragraph 67 to page 22, paragraph 71.

Accordingly, one skilled in the art, enlightened by teachings of the present application, could readily envision countless polypeptide sequences that comprise the specified polypeptides. For example, the skilled artisan could clearly envision each of the polypeptides that are 95% identical to the claimed amino acid lengths of SEQ ID NO:6 as a polypeptide with at least 1, 2, 3, 4, etc. amino acid substitutions or deletions along its length. Indeed, nothing more than a basic knowledge of the genetic code and what is described in the specification would be required for the skilled artisan to identify every single one of the polypeptides that are 95% identical to the claimed amino acid lengths of SEQ ID NO:6. Clearly, such knowledge is well within what is expected of the skilled artisan.

In addition, the above written description supports the open-ended language of claim 21. In particular, Applicants note that claim 21 is dependent from claim 9. Thus, a skilled artisan, using the teachings of the specification above, would readily be able to envision each and every polypeptide that is 95% identical to the claimed amino acid lengths of SEQ ID NO:6 and comprise the claimed polypeptide fragments.

Moreover, contrary to the Examiner's arguments, the specification discloses that the claimed polypeptides may be fused to heterologous polypeptides. For example, the specification discloses that the claimed polypeptides may be expressed in the form of a fusion protein that may include signal sequences or other heterologous functional regions. *See*, specification, at page 12, paragraph 37. The specification also discloses that the claimed polypeptides may be fused to various heterologous polypeptides, including but not limited to, peptide moieties to facilitate purification and improve stability, immunoglobulin to increase

solubilization, and polyethylene glycol to increase the half-life of the polypeptide. *See*, for example, specification at page 17, paragraph 55; at page 19, paragraph 60; and at page 24, paragraph 79.

Thus, the instant claims clearly distinguish the boundaries of each claimed genus and identify all of the members of each genus. Accordingly, one skilled in the art would reasonably conclude that Applicants had possession of the polypeptides encompassed by the rejected claims, upon reading the present application as filed.

Accordingly, from reading the specification, the skilled person would immediately recognize that, at the time the specification was filed, the Applicants had "invented what is claimed" (*Vas-Cath*, 935 F.2d at 1563); namely, a genus of proteins comprising polypeptides with 95% identity to the claimed amino acids of SEQ ID NO:6, wherein said polypeptides inhibit TNFR-1 and CD-95 induced apoptosis. Therefore, the specification contains an adequate written description of the claimed polypeptides. Accordingly, Applicants respectfully request that the Examiner's rejection of the claims 9, 13-17, and 19-23 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Conclusion

Applicants respectfully request that the above-made remarks be entered and made of record in the file history of the instant application. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicant would expedite the examination of this application.

If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Date: Dec. 20, 2004

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